

**Arsenic in drinking water and cerebrovascular disease, chronic airways obstruction,  
diabetes mellitus, and kidney disease in Michigan:  
a standardized mortality ratio analysis**

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## **Abstract**

**Background:** Exposure to arsenic concentrations in drinking water in excess of 300 µg/L is associated with diseases of the circulatory and respiratory system, several types of cancer, kidney diseases, and diabetes; however, little is known about the health consequences of exposure to low-to-moderate levels of arsenic (10-100 µg/L).

**Methods:** A standardized mortality ratio (SMR) analysis was conducted in a contiguous six county study area of southeastern Michigan to investigate the relationship between moderate arsenic levels and twenty-three selected disease outcomes. Arsenic data were compiled from 9251 well water samples tested by the Michigan Department of Environmental Quality from 1983 through 2002. Michigan Resident Death Files data were amassed for 1979 through 1997 and sex-specific SMR analyses were conducted with indirect adjustment for age and race; 99% confidence intervals (CI) were reported.

**Results:** The study area had an arithmetic mean arsenic concentration of 17.7 µg/L, with 10% of the samples exceeding 43.0 µg/L. In addition, 68% of the population in the study area was served by groundwater. Elevated mortality rates were observed for both males (M) and females (F) for all diseases of the circulatory system (M SMR: 1.11; CI: 1.09, 1.13; F SMR: 1.15; CI: 1.13, 1.17), cerebrovascular diseases (M SMR: 1.19; CI: 1.14, 1.25; F SMR: 1.19; CI: 1.15, 1.23), chronic airways obstruction (M SMR: 1.16; CI: 1.09, 1.24; F SMR: 1.14; CI: 1.05, 1.23), diabetes mellitus (M SMR: 1.28; CI: 1.18, 1.37; F SMR: 1.27; CI: 1.19, 1.35), and kidney diseases (M SMR: 1.28; CI: 1.15, 1.42; F SMR: 1.38; CI: 1.25, 1.52). Deaths from chronic liver diseases and cirrhosis were reduced (M SMR: 0.67; CI: 0.60, 0.74; F SMR: 0.87; CI: 0.77, 0.99).

**Conclusions:** This is some of the first evidence to suggest that exposure to low-to-

moderate levels of arsenic in drinking water may be associated with several of the leading causes of mortality, although further epidemiologic studies are required to confirm the results suggested by this ecologic SMR analysis.

## **Background**

Assessment of health risks associated with exposure to moderately elevated levels of arsenic in drinking water (10-100  $\mu\text{g/l}$ ) has become the subject of considerable interest and some controversy in both regulatory and public health communities. The United States Environmental Protection Agency (USEPA), for instance, recommended a reduction in the maximum contaminant level (MCL) to 10  $\mu\text{g/l}$  for arsenic in US public drinking water supplies [1] despite the conclusion made by the National Research Council subcommittee on Arsenic in Drinking Water that additional epidemiologic investigations are necessary to characterize the dose-response relationship at low doses for arsenic-associated cancer and non-cancer end points [2].

The call for a significant reduction in the MCL by the USEPA was prompted, at least in part, by findings of internal cancers (especially bladder, kidney, liver, and lung) among populations in Taiwan, Japan, Chile, and Argentina that are exposed to elevated levels of arsenic (typically  $> 300 \mu\text{g/l}$ ) in their drinking water [3-8]. In addition to cancer, ample evidence exists to support a relationship between arsenic in drinking water and cardiovascular and circulatory diseases such as blackfoot disease [9-10], ischemic heart diseases [11], and cerebrovascular diseases [12]. Emerging evidence also suggests an association between arsenic and diabetes mellitus [13-14] and nonmalignant respiratory diseases [15-16]. Most of these studies, however, examined arsenic concentrations of

300 µg/L and above, providing little insight into health effects from low-to-moderate concentrations (10-100 µg/L) which are more commonly found in sources of drinking water in the US and Europe.

A few mortality studies have been conducted in areas where arsenic concentrations in drinking water are commonly in the 10-100 µg/L range; however, a clear picture of the relevant health risks has not yet emerged. Engel and Smith (1994) conducted a standardized mortality ratio (SMR) analysis for vascular and respiratory diseases in thirty US counties with elevated levels of arsenic in drinking water. Diseases of arteries, arterioles, and capillaries (DAAC), emphysema, and chronic airways obstruction exhibited significantly elevated SMRs in counties where mean arsenic levels exceeded 20 µg/L. In a cohort mortality study in Millard County, Utah where arsenic levels ranged from 14-166 µg/L, Lewis et al. [17] examined cancer and a host of cardiovascular, respiratory, and kidney diseases. These authors reported significant positive SMRs for women and men from hypertensive heart diseases, and for only men from nephritis and nephrosis, and prostate cancer. In contrast to the results from Engel and Smith [10], however, Lewis et al [17] did not identify an elevated SMR for DAAC, and did not investigate deaths caused by emphysema or chronic airways obstruction. In ecologic studies conducted in Belgium [18] and Hungary [19], low-to-moderate levels of arsenic were not reported to be associated with mortality due to diseases of the nervous system, circulatory system, liver, or cancer. Individual-level incidence studies of low-to-moderate arsenic exposure have also generated ambiguous findings with regard to the role of arsenic in cancers of the bladder and skin [20-25].

In light of this uncertainty, it is important to continue to investigate health risks

from exposure to arsenic concentrations in the 10-100 µg/L range. Therefore, the goal of this study is to investigate mortality rates for twenty-three different health outcomes, including several types of cancer, circulatory and respiratory diseases, diabetes, and diseases of the kidneys and liver in six contiguous counties of Michigan with moderately elevated levels of arsenic in drinking water.

## **Methods**

### ***Arsenic in southeastern Michigan study area***

Elevated concentrations of arsenic in Michigan groundwater were first reported from a well supplying a mobile home park in Huron County in 1981 [26]. Since then, arsenic has been identified in groundwater supplies, typically in the 10-100 µg/L range, throughout six contiguous counties of Michigan and is now a well-documented phenomenon that has generated considerable concern [27-29]. The counties involved include Genesee, Huron, Lapeer, Sanilac, Shiawassee, and Tuscola, and are located in the Michigan thumb region (Figure 1). The 2000 US Census indicates the six counties have a population of approximately 740,000 people and occupy an area of approximately 11,500 km<sup>2</sup>. The majority of the population resides in Genesee County (439,000), while the remainder is split fairly evenly among the other five counties.

Estimates of arsenic concentrations in drinking water in the six-county study area were compiled from the Michigan Department of Environmental Quality (MDEQ) arsenic database which contains results from water samples collected and analyzed between 1983 and 2002. The database includes 9,251 analyses of water samples from the six-county study area while the other 23,691 analyses were conducted throughout the remainder of

the state (Table 1). The six counties of interest contain arsenic concentrations  $\geq 10 \mu\text{g/L}$  in 50% of the samples analyzed, with 68% of the population served by groundwater. In comparison, 18% of the samples analyzed in the remainder of Michigan contain arsenic concentrations  $\geq 10 \mu\text{g/L}$ , with 44% of the population served by groundwater. Those not drinking groundwater are served by municipal surface water from the Great Lakes which contains arsenic concentrations below  $1 \mu\text{g/L}$  [30].

The MDEQ arsenic database is comprised of samples analyzed using various methodologies including graphite furnace atomic absorption spectrometry (GF/AAS) (1983-1987, 1989-1995), inductively coupled plasma (ICP) optical emission hydride generation (1987-1988), hydride flame (quartz tube AAS) (1989-1995), and ICP/mass spectrometry (1996-present). Approximately 86% of the analyses were of private wells, and 14% came from municipal wells. Analyses of water samples from private wells were performed at the request of property owners, and previous analyses have indicated that samples analyzed using different methods were highly correlated [31].

### ***Mortality and Population Data***

Cause-specific mortalities from 1979 to 1997 were compiled from Michigan Resident Death Files by the Vital Records and Health Data Development Section of the Michigan Department of Community Health (MDCH). Twenty-three different underlying causes of death were included in the study, categorized according to the International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9). The twenty-three causes of death include several types of cancer, diseases of the circulatory and respiratory system, diabetes mellitus, and kidney and liver diseases, and are listed in Table 2. Each of these

diseases has shown some evidence of association with arsenic exposure, although at higher concentrations in drinking water. The number of deaths from 1979 through 1997 by cause in each individual county and in the entire State were stratified by sex, race, and age and grouped into five-year categories beginning at age 35 and ending at  $\geq 85$  years of age. Census data and population estimates were compiled at five-year time intervals from the same period for the State of Michigan and the six counties in the study area.

### ***Data Analysis***

Sex-specific SMRs were calculated for the six-county study area by dividing the number of observed deaths from a given cause by the age- and race-adjusted expected values for Michigan [32]. Expected values were calculated using indirect adjustment; statewide mortality rates for each underlying cause, stratified by age, race, and sex were multiplied by the combined sex-, race-, and age-specific person-years in each county. To account for the large number of calculations (23 SMRs each for males and females), 99% confidence intervals, instead of 95%, were calculated.

### **Results**

SMRs are reported for twenty-three causes of death for males and females in the six county area of southeastern Michigan (Table 2). Observed deaths from cancers were not different from the expected values for males or females, with the exception of cancer of the female reproductive organs (ICD-9 179-184), which was elevated.

Deaths from all diseases of the circulatory system (ICD-9 390-459) and cerebrovascular diseases (ICD-9 430-438) were elevated in both males and females. In

females only, deaths from atherosclerosis (ICD-9 440) were elevated and deaths from aortic aneurysm (ICD-9 441) were reduced.

Deaths from respiratory diseases were elevated in the study area, with chronic airways obstruction-related deaths elevated in both males and females (ICD-9 496). Males also experienced elevated mortality rates for all diseases of the respiratory system (ICD-9 460-519).

Deaths from diabetes mellitus (ICD-9 250) and kidney diseases (ICD-9 580-589) were also elevated among both males and females in the study area. Deaths from chronic liver diseases and cirrhosis (ICD-9 571) were reduced for males and females.

## **Discussion**

In the counties of the Michigan thumb region with moderately elevated levels of arsenic in drinking water, heightened mortality rates were observed for diabetes mellitus, cerebrovascular diseases, kidney diseases, and chronic airways obstruction in both males and females. Each of these health endpoints is reported to be associated with arsenic in drinking water at levels in excess of 200-300  $\mu\text{g/L}$ ; here we present some of the first evidence of a relationship between these health outcomes and arsenic concentrations in a region of the US where elevated concentrations typically range from 10-100  $\mu\text{g/L}$ .

Arsenic has been shown to be associated with increased rates of diabetes incidence [14], prevalence [13,33], and mortality [8] in studies from Taiwan and Bangladesh. Only one previous study, however, examined risk of diabetes from drinking water arsenic concentrations below 200  $\mu\text{g/L}$  and that study found no association [17]. In contrast, we report elevated mortality rates for diabetes in both males (SMR: 1.28;

99%CI: 1.18, 1.37) and females (SMR: 1.27; 99%CI: 1.19, 1.35). This inconsistency may be explained by the added power in our study which includes 1249 male and 1612 female deaths from diabetes, compared with only 20 male and 35 female deaths in the study by Lewis et al. [17]. Diabetes mellitus is a complex disease, defined as a set of abnormalities characterized by a state of sustained hyperglycemia. It is the sixth leading cause of death in the United States, with unknown specific etiology [34-35]. The features of diabetes mellitus most commonly observed in arsenic-exposed individuals are similar to non-insulin-dependent diabetes mellitus or Type 2 diabetes [14]. Although the biological mechanisms responsible for arsenic-induced diabetes mellitus are largely unknown, recent evidence suggests that the trivalent arsenicals may suppress insulin-stimulated glucose uptake by interfering with mobilization of glucose transporters in adipose cells [36], as well as interfering with transcription factors involved in insulin-related gene expression [37].

In addition to diabetes, elevated mortality rates were observed for cerebrovascular diseases for males (SMR: 1.19; 99%CI: 1.14, 1.25) and females (SMR: 1.19; 99%CI: 1.15, 1.23). Elevated mortality rates were also observed when grouping together all diseases of the circulatory system, however, only mortality from cerebrovascular diseases was elevated when examining the individual major causes of vascular-related death. Cerebrovascular diseases are the third leading cause of death in the United States [35]. Epidemiologic studies have previously reported increased prevalence [12] and mortality [8] from cerebrovascular diseases in high arsenic areas of Taiwan. Chiou et al. [12] found prevalence of cerebrovascular diseases to be significantly associated with arsenic levels as low as 0.1-50 µg/L in drinking water (compared to a baseline of <0.1 µg/L).

Increased mortality from cerebrovascular diseases, however, was not found in previous ecologic studies of health effects from low-to-moderate arsenic exposure in the US [10,17]. In fact, Lewis et al. [17] reported a marginally significant protective effect from arsenic on cerebrovascular diseases for males (SMR=0.79; 95% CI: 0.62, 0.99), but not a significantly protective effect for females. The Utah study, however, relied on data from a cohort of members of the Church of Jesus Christ of Latter-day Saints whose personal lifestyle choices (e.g., no tobacco smoking or consumption of alcohol) made comparison with other study populations difficult, especially with regard to cerebrovascular and other heart diseases. Experimental studies suggest potential mechanisms for cerebrovascular toxicity of arsenic include inflammatory and coagulatory activity of endothelial cells, increased oxidative stress, and impaired vascular nitric oxide homeostasis [38]. These studies, however, have typically been performed using unrealistically high arsenic concentrations calling into question their mechanistic relevance [39]. Our study lends support to the evidence that low-to-moderate levels of arsenic in drinking water are associated with elevated rates of cerebrovascular diseases.

Kidney diseases are the ninth leading cause of death in the United States [35] and were also found to be elevated in the six-county study area for males (SMR: 1.28; 99%CI: 1.15, 1.42) and females (SMR: 1.38; 99%CI: 1.25, 1.52). Elevated mortality rates for kidney diseases have been reported in high arsenic areas of Taiwan [8], and significantly elevated SMRs were also reported from nephritis and nephrosis (SMR=1.72; 95% CI: 1.13, 2.50) in Utah men [17]. Few mechanisms of arsenic-induced kidney diseases have been proposed, however. Kidney diseases, like cerebrovascular diseases, are a frequent complication of diabetes, and arsenic may be affecting the kidney via vascular changes

associated with diabetes.

Chronic lower respiratory diseases are the fourth leading cause of death in the United States [35] and diseases of chronic airways obstruction, a large component of chronic lower respiratory diseases, were elevated in males (SMR: 1.16; 99% CI: 1.09, 1.24) and females (SMR: 1.14; 99% CI: 1.05, 1.23) in our study area. Higher than expected prevalence rates for chronic cough and bronchiectasis have previously been reported in high arsenic regions of Bangladesh [15-16] and elevated mortality rates for chronic airways obstruction were also observed in a previous ecologic study of low-to-moderate arsenic exposure in the US [10]. Coupled with reports of arsenic in drinking water being associated with lung cancer [6], our study contributes to an emerging body of evidence that ingested arsenic is a respiratory toxicant and carcinogen. Despite the recent epidemiologic evidence of an association between arsenic ingestion and respiratory ailments, the pathophysiologic mechanisms behind such an association are not yet understood.

A few additional disease outcomes were marginally significant for one sex but not the other: atherosclerosis (SMR: 1.11; 99% CI: 1.02, 1.21) and aortic aneurysm (SMR: 0.81; 99% CI: 0.67, 0.96) in females, and all diseases of the respiratory system among males (SMR: 1.05; 99% CI: 1.01, 1.09). Additional evidence is needed to assess the importance of these findings. As well, deaths from cancer of the female reproductive organs were significant (SMR: 1.11; 99% CI: 1.03, 1.19). Mortality from cervical cancer was elevated in a Taiwanese study [8], however, the evidence for a relationship between arsenic exposure and cervical cancer is not nearly as strong as that with other cancers. The lack of findings of significantly elevated mortality rates for cancers of the bladder,

kidney, lung, and skin in our study might suggest that arsenic levels in groundwater of southeastern Michigan are below the threshold for cancer induction, or there may be moderating factors which were not considered here. In addition, the use of mortality rates may not be the best measure for certain cancer outcomes, such as skin and bladder cancer, which have relatively high survival rates [40].

Reduced mortality rates were observed for chronic liver diseases and cirrhosis for both males (SMR: 0.67; 99% CI: 0.60, 0.74) and females (SMR: 0.87; 99% CI: 0.77, 0.99). This is surprising since arsenic is a well-established risk factor for liver diseases when high doses are given in animal studies [41]. It is possible that low-to-moderate levels of arsenic in drinking water are protective against liver diseases; however, a more likely explanation is the lower rates of alcohol consumption in this region of Michigan. Michigan Behavioral Risk Factor Survey (BRFS) data from 1989-1993 (Table 3) indicate lower age-adjusted rates of heavy or binge drinking from this part of Michigan, as compared to the state as a whole [42].

In addition to alcohol consumption, other differences in demographics and risk factors between this part of Michigan and the State as a whole may influence interpretation of the results. The study area contained a higher percentage of people who were living below the poverty level, and a lower percentage of people who graduated from college with a bachelor's degree (Table 3) [43]. However, only a small difference was reported between median household income in the study area and that of the State. The study area also contained more people who reported their race to be white, and is considerably more rural than the State as a whole. BRFS data generally indicate poorer access to health care in the most rural parts of the State [42], however higher rates of

mammography and cholesterol screening were reported in this part of Michigan compared with the State average. It is unknown how these rates relate to screening for other diseases. A slightly higher prevalence of cardiovascular disease risk factors such as obesity, high blood pressure, and high cholesterol has also been reported in the study area. Smoking prevalence in the study area, however, is no different than that of the state as a whole. Obesity, high blood pressure, cigarette smoking, and poor access to health care are established risk factors for the diseases of strongest significance here [44-45], however not all of these factors are elevated in the study area. Furthermore, deaths due to other diseases strongly associated with these risk factors, such as emphysema, lung cancer, ischemic heart diseases, and DAAC were not elevated in our study suggesting that smoking, poor access to health care, obesity, and high blood pressure alone can only partially explain the elevated mortality rates observed for kidney and cerebrovascular diseases, diabetes mellitus, and chronic airways obstruction.

In addition to differences in the prevalence of risk factors and confounding variables between the six county study area and the entire state of Michigan, other aspects of the study deserve consideration. This study did not assess the accuracy and precision of the arsenic laboratory measurements nor the proportion of each arsenic species (As(III) and As(V)) in the drinking water samples. This study also did not investigate differences in the reporting and classification of underlying causes of death across counties and regions. Such reporting and classification differences are common in mortality studies of diabetes [46]; however, these differences are less common for mortality studies of kidney and cerebrovascular diseases, and chronic airways obstruction [47].

Additional limitations characteristic of ecologic studies also need to be kept in mind when interpreting our results: individual-level exposure has not been assessed; mortality in one geographic area does not imply that a person lived there for long periods of his or her life; and confounding variables such as smoking and obesity were not included in the quantitative analyses. Since there is no individual-level exposure assessment, interpretation of exposure at the individual-level would result in the Berkson measurement error [48]. Furthermore, as is forewarned by the ecologic fallacy, conclusions should not be drawn at the individual-level because there was no individual-level assessment of the exposure-disease relationship, only a county-level assessment.

## **Conclusions**

These limitations notwithstanding, this region of southeastern Michigan was selected because of moderately elevated concentrations of arsenic in groundwater, a large percentage of the population using groundwater as their drinking water source (Table 1), and low rates of migration in and out of the study area [31]. Health risks from long-term ingestion of water containing arsenic concentrations in the 10-100  $\mu\text{g/L}$  range are uncertain, and this ecologic study is a first step in suggesting that moderately elevated arsenic concentrations are associated with mortality from cerebrovascular diseases, diabetes mellitus, chronic airways obstruction, and kidney diseases. Carefully planned individual-level epidemiologic studies are necessary to further investigate this relationship.

## **List of Abbreviations Used**

AAS	Atomic Absorption Spectrometry
BRFS	Behavioral Risk Factor Survey
DAAC	Diseases of Arteries, Arterioles, and Capillaries
EPA	Environmental Protection Agency
GF	Graphite Furnace
ICD-9	International Classification of Diseases, 9 <sup>th</sup> Revision
ICP	Inductively Coupled Plasma
MCL	Maximum Contaminant Level
MDCH	Michigan Department of Community Health
MDEQ	Michigan Department of Environmental Quality
SMR	Standardized Mortality Ratio

## **Competing Interests**

The authors declare that they have no competing interests.

## **Authors' Contributions**

LC and RW conceived of and designed this study; RW gained access to the data and oversaw data coding and data management. JM conducted the analyses and drafted the manuscript. JN, LC, and RW offered analytical suggestions, assisted with interpretation, made critical revisions to the manuscript, and gave approval to the final draft.

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## References

1. USEPA: *National Primary Drinking Water Regulations: Arsenic and clarifications to compliance and new source contaminants monitoring; final rule*. Fed Reg, 66(no. 14): 6976-7066; 2001.
2. NRC: *Arsenic in Drinking Water*. National Academy of Sciences Press, Washington, D.C; 1999.
3. Ferreccio C, Gonzalez C, Milosavjevic V, Marshall G, Sancha AM, Smith AH: **Lung cancer and arsenic concentrations in drinking water in Chile**. *Epidemiology* 2000, **11**:673-679.
4. Guo H-R, Chiang H-S, Hu H, Lipsitz SR, Monson RR: **Arsenic in drinking water and incidence of urinary cancers**. *Epidemiology* 1997, **8**:545-550.
5. Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, Smith AH: **Bladder cancer mortality associated with arsenic in drinking water in Argentina**. *Epidemiology* 1996, **7**:117-124.
6. Smith AH, Goycolea M, Haque R, Biggs ML: **Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water**. *Am J Epidemiol* 1998, **147**:660-669.
7. Steinmaus C, Moore L, Hopenhayn-Rich C, Biggs ML, Smith AH: **Arsenic in drinking water and bladder cancer**. *Cancer Invest* 2000, **18**:174-182.
8. Tsai S-M, Wang T-N, Ko Y-C: **Mortality for certain diseases in areas with high levels of arsenic in drinking water**. *Arch Environ Health* 1999, **54**:186-193.

9. Ch'i IC, Blackwell RQ: **A controlled retrospective study of blackfoot disease, an endemic peripheral gangrene disease in Taiwan.** *Am J Epidemiol* 1968, **88**:7-24.
10. Engel RR, Smith AH: **Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States.** *Arch Environ Health* 1994, **49**:418-427.
11. Chen C-J, Chiou H-Y, Chiang M-H, Lin L-J, Tai T-Y: **Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure.** *Arterioscl Throm Vas* 1996, **16**:504-510.
12. Chiou H-Y, Huang W-I, Su C-L, Chang S-F, Hsu Y-S, Chen C-J: **Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic.** *Stroke* 1997, **28**:1717-1723.
13. Rahman M, Tondel M, Ahmad SK, Axelson O: **Diabetes mellitus associated with arsenic exposure in Bangladesh.** *Am J Epidemiol* 1998, **148**:198-203.
14. Tseng C-H, Tai T-Y, Chong C-K, Tseng C-P, Lai M-S, Lin BJ, Chiou H-Y, Hsueh Y-M, Hsu K-H, Chen C-J: **Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: A cohort study in arseniasis-hyperendemic villages in Taiwan.** *Environ Health Persp* 2000, **108**:847-851.
15. Mazumder DNG, Steinmaus C, Bhattacharya P, von Ehrenstein OS, Ghosh N, Gotway M, Sil A, Balmes JR, Haque R, Hira-Smith MM, Smith AH: **Bronchiectasis in persons with skin lesions resulting from arsenic in drinking water.** *Epidemiology* 2005, **16**:760-765.
16. Milton AH, Rahman M: **Respiratory effects and arsenic contaminated well water in Bangladesh.** *Int J Environ Health R* 2002, **12**:175-179.

17. Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rench J, Calderon RL: **Drinking water arsenic in Utah: A cohort mortality study.** *Environ Health Persp* 1999, **107**:359-365.
18. Buchet JP, Lison D: **Mortality by cancer in groups of the Belgian population with a moderately increased intake of arsenic.** *Int Arch Occup Environ Health* 1998, **71**:125-130.
19. Varsanyi I, Fodre Z, Bartha A: **Arsenic in drinking water and mortality in the southern Great Plain, Hungary.** *Environ Geochem Hlth* 1991, **13**:14-22.
20. Bates MN, Smith AH, Cantor KP: **Case-control study of bladder cancer and arsenic in drinking water.** *Am J Epidemiol* 1995, **141**:523-530.
21. Bates MN, Rey OA, Biggs ML, Hopenhayn C, Moore LE, Kalman D, Steinmaus C, Smith AH: **Case-control study of bladder cancer and exposure to arsenic in drinking water in Argentina.** *Am J Epidemiol* 2004, **159**:381-389.
22. Karagas MR, Stukel TA, Morris JS, Tosteson TD, Weiss JE, Spencer SK, Greenberg ER: **Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study.** *Am J Epidemiol* 2001, **153**:559-565.
23. Karagas MR, Tosteson TD, Morris JS, Demidenko E, Mott LA, Heaney J, Schned A: **Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire.** *Cancer Cause Control* 2004, **15**:465-472.
24. Michaud DS, Wright ME, Cantor KP, Taylor PR, Virtamo J, Albanes D: **Arsenic concentrations in prediagnostic toenails and the risk of bladder cancer in a cohort study of male smokers.** *Am J Epidemiol* 2004, **160**:853-859.

25. Steinmaus C, Yuan Y, Bates MN, Smith AH: **Case-control study of bladder cancer and drinking water arsenic in the western United States.** *Am J Epidemiol* 2003, **158**:1193-1201.
26. Michigan Department of Public Health: *Arsenic in drinking water -- A study of exposure and clinical survey.* Division of Environmental Epidemiology, Michigan Department of Public Health, Lansing, MI; 1982.
27. Haack SK, Trecanni SL: *Arsenic concentration and selected geochemical characteristics for ground water and aquifer materials in southeastern Michigan.* US Geological Survey Water Resources Investigation Report 00-4171; 2000.
28. Kim MJ, Nriagu JO, Haack S: **Arsenic species and chemistry in groundwater of southeast Michigan.** *Environ Pollut* 2002, **120**:379-390.
29. Kolker A, Haack SK, Cannon WF, Westjohn DB, Kim MJ, Nriagu J, Woodruff LG: **Arsenic in southeastern Michigan.** In *Arsenic in Ground Water* Edited by Welch AH and Stollenwerk KG. Norwell, Massachusetts: Kluwer Academic Publishers; 2003:281-294.
30. Slotnick MJ, Meliker JR, Nriagu JO: **Effects of Time and Point-of-Use Devices on Arsenic Levels in Southeastern Michigan Drinking Water, USA.** *Sci Tot Environ*, in press.
31. Meliker JR, Slotnick MJ, AvRuskin GA, Kaufmann A, Fedewa SA, Goovaerts P, Jacquez GM, Nriagu JO: **Individual lifetime exposure to inorganic arsenic using a Space-Time Information System.** *Int Arch Occup Environ Health*, in press.

32. Breslow NE, Day NE: *Statistical methods in cancer research. Vol II: the design and analysis of cohort studies*. Lyon, France: IARC Scientific publications No. 82; 1987.
33. Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, Wu MM, Tai TY: **Ingested inorganic arsenic and prevalence of diabetes mellitus**. *Am J Epidemiol* 1994, **139**:484-492.
34. American Diabetics Association: **Standards of Medical Care in Diabetes**. *Diabetic Care* 2005, 28 **Suppl 1**:S4-S36.
35. Anderson RN, Smith BL: **Deaths: leading causes for 2002**. *National Vital Statistics Reports* 2005, **53**:17.
36. Walton FS, Harmon AW, Paul DS, Drobna Z, Patel YM, Styblo M: **Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes**. *Toxicol Appl Pharmacol* 2004, **198**:424-433.
37. Salazard B, Bellon L, Jean S, Maraninchi M, El Yazidi C, Orsiere T, Margotat A, Botta A, Bergé-Lefranc J-L: **Low-level arsenite activates the transcription of genes involved in adipose differentiation**. *Cell Biol Toxicol* 2004, **20**:375-385.
38. Simeonova PP, Luster MI: **Arsenic and atherosclerosis**. *Toxicol Appl Pharmacol* 2004, **198**:444-449.
39. Navas-Acien A, Sharrett AR, Silbergeld EK, Schwartz BS, Nachman KE, Burke TA, Guallar E: **Arsenic exposure and cardiovascular disease: a systematic review of the epidemiological evidence**. *Am J Epidemiol* 2005, **162**:1037-49.
40. Adami H-O, Hunter D, Trichopoulos D: *Textbook of Cancer Epidemiology*. New York: Oxford University Press; 2002.

41. Liu T, Liu J, LeCluyse EL, Zhou YS, Cheng ML, Waalkes MP: **Application of cDNA microarray to the study of arsenic-induced liver diseases in the population of Guizhou, China.** *Toxicol Sci* 2001, **59**:185-192.
42. Schillo BA, Skarupski KA, McGee H, Rafferty A: *Michigan Risk Factor Surveillance System: Assessing Risk Factors at the Regional Level 1989-1993*. Michigan Dept. of Public Health, Center for Health Promotion and Disease Prevention, Lansing MI; 1995.
43. US Census Bureau. **Census 1990.** [<http://factfinder.census.gov>] Accessed December 16, 2005.
44. Paeratakul S, Lovejoy JC, Ryan DH, Bray GA: **The relation of gender, race and socioeconomic status to obesity and obesity comorbidities in a sample of US adults.** *Int J Obesity* 2002, **26**:1205-1210.
45. Sturm R: **The effects of obesity, smoking, and drinking on medical problems and costs.** *Health Affairs* 2002, **21**:245-253.
46. Morgan CL, Currie CJ, Peters JR: **Relationship between diabetes and mortality: a population study using record linkage.** *Diabetes Care* 2000, **23**:1103-7.
47. Hansell A, Hollowell J, McNiece R, Nichols T, Strachan D: **Validity and interpretation of mortality, health service and survey data on COPD and asthma in England.** *Eur Respir J* 2003, **21**:279-286.
48. NRC: *Arsenic in Drinking Water: 2001 Update*. National Academy of Sciences Press, Washington DC; 2001.



## **Figure Legends**

Figure 1: The six-county study area in the “thumb” region of southeastern Michigan, where arsenic concentrations in groundwater frequently exceed 10 µg/L.

## Tables and captions

Table 1: Arsenic Concentration in Drinking Water in Michigan

	Mean Arsenic Concentration (µg/L)	Median Arsenic Concentration (µg/L)	90 <sup>th</sup> Percentile Arsenic Concentration (µg/L)	Number of Groundwater Samples	% of Samples ≥ 10 µg/L	% of Population Drinking Groundwater	Population Size
Six County Study Area	17.7	9.5	43.0	9251	50%	68%	740,000
Remainder of Michigan	6.4	2.5	17.0	23691	18%	44%	9,300,000

Collected from 1983-2002, from Michigan Department of Environmental Quality; US Maximum Contaminant Level for public drinking water supplies is 10 µg/L.

Table 2: Standardized Mortality Ratios for Males and Females in Six Michigan Counties with Elevated Levels of Arsenic in Drinking Water, 1979-1997.

Cause of Death	ICD-9	Males			Females		
		Obs	SMR	99% CI	Obs	SMR	99% CI
<b>CANCERS</b>							
Colon and rectum	153-154	1439	1.04	0.97, 1.11	1369	1.03	0.96, 1.10
Liver and biliary Passages	155-156	260	0.85	0.72, 1.00	300	1.04	0.89, 1.20
Trachea, bronchus and lung	162	4425	1.02	0.98, 1.06	2297	1.02	0.96, 1.07
Skin melanoma	172	143	0.99	0.79, 1.22	91	0.97	0.73, 1.27
Other skin cancer	173	59	1.24	0.86, 1.72	26	1.06	0.60, 1.72
Female reproductive Organs	179-184				1300	1.11*	1.03, 1.19
Prostate	185	1448	1.03	0.96, 1.10			
Bladder	188	348	0.94	0.82, 1.08	171	0.98	0.80, 1.19
Kidney and other urinary organs	189	325	1.06	0.91, 1.22	194	1.00	0.82, 1.20
<b>CIRCULATORY DISEASES</b>							
All diseases of the circulatory system	390-459	25907	1.11*	1.09, 1.13	26699	1.15*	1.13, 1.17
Essential hypertension and hypertensive renal disease	401, 403	203	1.16	0.96, 1.38	250	1.01	0.85, 1.18
Hypertensive heart disease and hypertensive heart and renal disease	402, 404	398	0.88	0.77, 1.00	612	1.01	0.91, 1.12
Ischemic heart diseases	410-414	14073	1.01	0.99, 1.03	12573	1.01	0.98, 1.03
Cerebrovascular diseases	430-438	3493	1.19*	1.14, 1.25	5010	1.19*	1.15, 1.23
Diseases of arteries arterioles and capillaries (DAAC)	440-448	1220	1.01	0.93, 1.08	1329	1.04	0.97, 1.11
Atherosclerosis	440	523	1.01	0.90, 1.13	884	1.11*	1.02, 1.21
Aortic aneurysm	441	504	0.95	0.85, 1.07	212	0.81*	0.67, 0.96
<b>RESPIRATORY DISEASES</b>							
All diseases of the respiratory system	460-519	4433	1.05*	1.01, 1.09	3568	1.03	0.98, 1.07
Emphysema	492	632	1.00	0.90, 1.11	363	0.98	0.85, 1.12
Chronic airways Obstruction	496	1706	1.16*	1.09, 1.24	1134	1.14*	1.05, 1.23
<b>OTHER DISEASES</b>							
Diabetes mellitus	250	1249	1.28*	1.18, 1.37	1612	1.27*	1.19, 1.35
Chronic liver diseases and cirrhosis	571	632	0.67*	0.60, 0.74	416	0.87*	0.77, 0.99
Kidney diseases	580-589	614	1.28*	1.15, 1.42	679	1.38*	1.25, 1.52

ICD-9=International Classification of Diseases, 9<sup>th</sup> Revision; Obs=Number of observed deaths; CI=confidence interval; \*p<0.01.

Table 3: Prevalence of Selected Demographic Characteristics of Six County Study Area and Entire State of Michigan

	Six County Study Area	Entire State of Michigan
*Persons below poverty level (%)	17.0%	15.1%
*Population (above age 20) with bachelor's degree (%)	11.2%	17.2%
*White race (%)	86.0%	73.5%
*Median household income (US\$)	\$30,332	\$31,020
*Residing in a rural area	43.6%	29.5%
#Current smoking	25.1%	25.1%
#Heavy drinking (60+ drinks/mo)	2.6%	3.7%
#Binge drinking (5+ drinks on 1+ occasions in past month)	7.6%	11.7%
#Cholesterol never checked	16.1%	19.3%
#Ever told cholesterol high (among tested)	37.4%	33.0%
#Ever told high blood pressure	33.6%	31.4%
#Overweight (BMI $\geq$ 27.8 for men, $\geq$ 27.3 for women)	34.6%	33.4%
#Never had mammogram (among women 40+)	19.0%	22.2%

\*From US Census, 1990.

#From Michigan Behavioral Risk Factor Survey, 1989-1993; age-adjusted.

# Michigan

## Six County Study Area

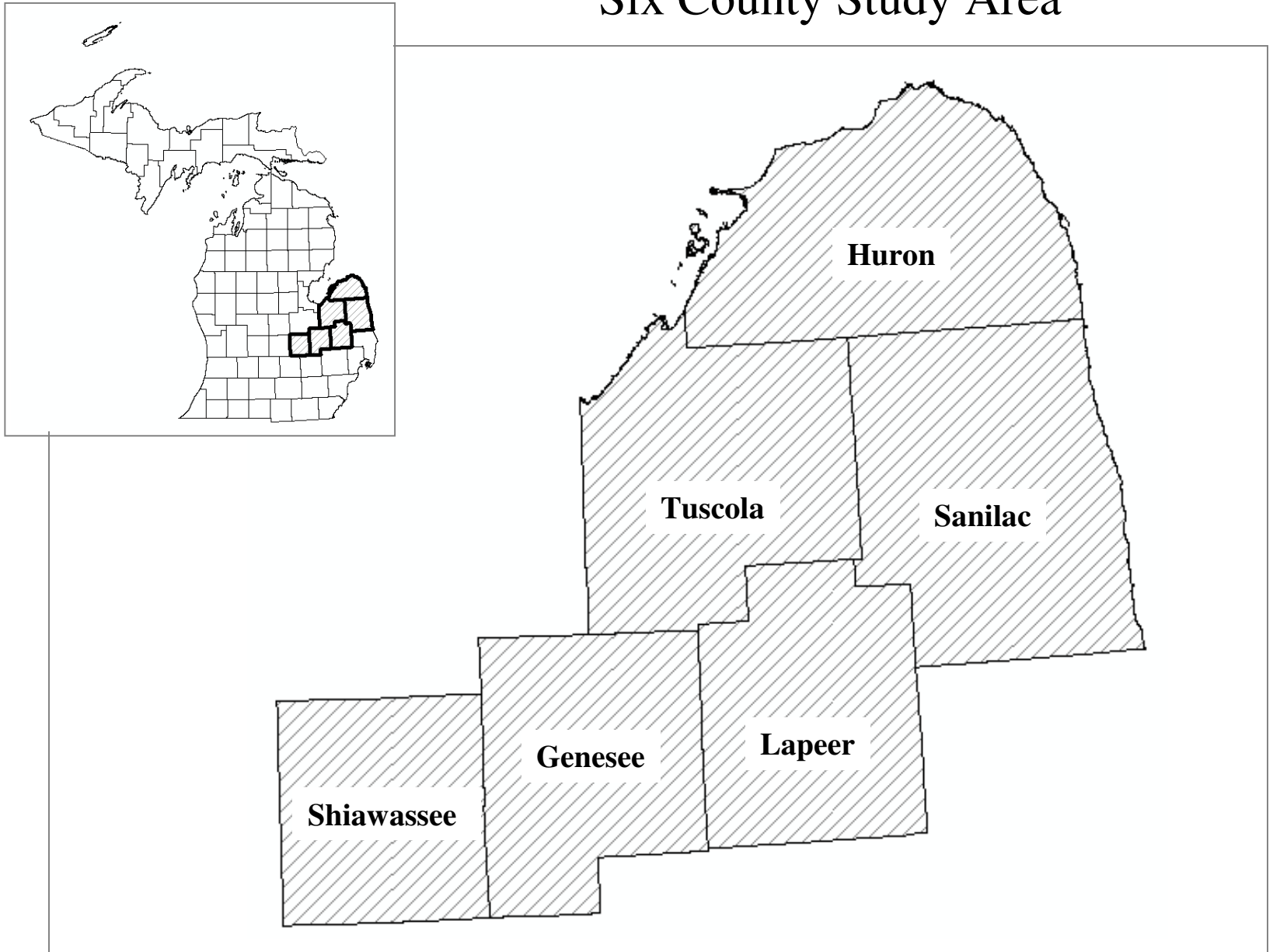


Figure 1